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A divergent and selective synthesis of *ortho*- and *para*-quinones from phenols

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ABSTRACT

We describe a divergent synthesis of substituted *ortho*- and *para*-quinones by catalytic aerobic oxygenation of phenols. Substituted quinones are omnipresent in chemistry and biology, but their synthesis frequently suffers from low efficiency and poor scope. Our methodology employs a catalytic aerobic di-functionalization of phenols to aryloxy-*ortho*-quinones. Regioselective substitution with an alcohol provides the alkoxy substituted *ortho*- or *para*-quinone, while hydrolysis affords the *para*-hydroxyquinone. These are mild and selective conditions for the synthesis of diversely substituted quinones from readily available phenol starting materials.

1. Introduction

ortho- and *para*-Quinones are fundamentally important to biochemical processes that include cellular respiration, melanogenesis, and blood coagulation.[1,2] They possess unique photo-physical properties and are important chromophores in natural and synthetic dyes.[3] They are a common pharmacophore in natural products,[4] and are of interest to the pharmaceutical industry.[5] They are also redox active, making them important components of enzymatic processes[6] and bio-mimetic catalysts.[7] Their reactivity can be finely tuned by substituents on the quinoidal ring, while their arrangement as either *ortho*- or *para*-isomer can have a dramatic impact on their overall physical properties.[8]

An important sub-class of *ortho*- and *para*-quinones are those which bear oxygen substituents (Fig. 1a).[1b,4c,9] Biologically active examples include the tanshinone quinones (cryptotanshinone and tanshinone IIA), which are prevalent in traditional Chinese medicine.[10] Coenzyme Q10 is a facilitator of electron transport in the mitochondria,[2e,11] and atovaquinone (Mepron) is used for the treatment of pneumocystis pneumonia.[12] Examples of alkoxyquinones in enzymatic catalysis are well-known, and include topaquinone in the active site of amine oxidase.[13] The mechanism of amine oxidase has inspired Stahl and Luo to develop *para*- and *ortho*-quinones (**5a**, **2a**, and **2b**) as biomimetic organocatalysts, which display complementary selectivity in the aerobic oxidation of amines (Fig. 1b).[8,13b,14] Finally, quinones are important intermediates for synthesis,[1b,9,15] as exemplified by the hetero-[4+2] cycloaddition of benzyloxy-*ortho*-quinone **6**, which created the unique macrocycle of sporolide B in Nicolau's classic total synthesis (Fig. 1c).[16]

In spite of their widespread occurrence, quinones can be difficult to prepare since they are redox active, electrophilic, and good ligands for a range of transition metals.[17] Their synthesis from phenol, catechol or resorcinol derivatives requires C–H oxygenation as well as de-aromatization. This is possible with a range of oxidants, although yields, selectivity, and scope are limited (Scheme 1a).[13b,18] Milder and higher-yielding oxidations occur for hydroxyquinols, but the synthesis of differentially protected polyphenols can require intricate protecting group manipulations.[16,19] Thus, the more facile oxidation of an oxygenated starting material can be offset by the difficulty of its synthesis.

In considering these challenges, we were drawn to a synthesis of alkoxyquinones reported by Maumy,[20] in which oxygenative coupling of 4-methoxy-phenol (**4l**) and substitution of the resulting *ortho*-quinone **1h** with an alcohol afforded di-alkoxyquinones (Scheme 1b). While the methodology was only demonstrated with **1h**, it demonstrated that an isohypsic substitution could introduce a range of oxygen nucleophiles under relatively mild conditions. We reasoned that this synthesis could be developed into a general methodology, with the potential to

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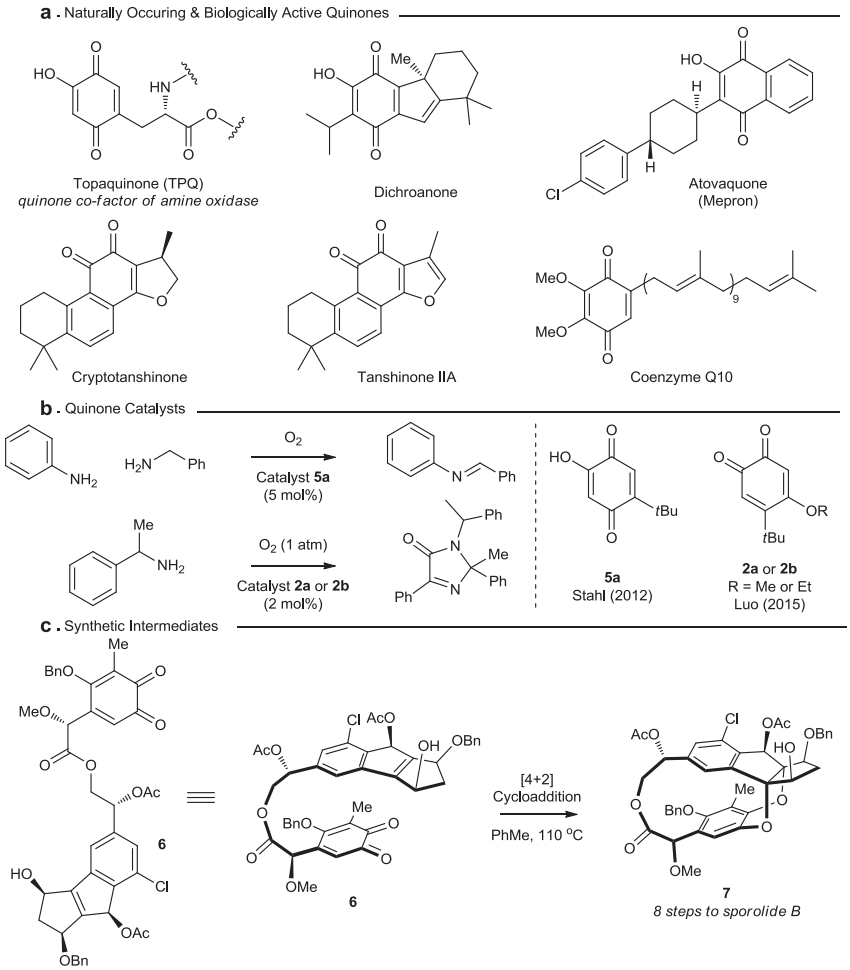

Fig. 1. Important *ortho*- and *para*-alkoxyquinones and *para*-hydroxyquinones in biology and chemistry.

access either *ortho*- or *para*-isomer directly from phenols under mild conditions (Scheme 2). Our strategy relies on a catalytic aerobic alternative to Maumy's stoichiometric oxygenative coupling, which we reported recently.[21] Based on Maumy's precedent, we expected that a substitution of **1a** with alcohols under basic conditions would provide 4-alkoxy-*ortho*-quinones, where diversity at R_1 would be derived from readily available phenol starting materials. Under acidic conditions, we suspected that substitution would provide the thermodynamically favored *para*-isomer, affording either configuration of the quinone in a two-step process from the phenol.

2. Results and discussion

As a point of departure, we revisited Maumy's conditions[20] for alcohol substitution using model quinone **1a**, catalytic quantities of base and methanol (MeOH) (Table 1). Using 10 mol % of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), the substitution was optimized to a 94% yield of **2a** when tetrahydrofuran (THF) was used as the solvent at a concentration of 0.5 M relative to **1a** (entry 2). Maumy had also chosen DBU as base, which is more effective than triethylamine, DBED or cesium carbonate (entries 5–7), but had employed a full equivalent and used a 3:1 mixture of acetonitrile and propionitrile as solvent.

The transformation of 4-aryloxy-*ortho*-quinones into *para*-alkoxyquinones is not known, so we began by investigating the substitution with MeOH under acidic conditions (Table 1). In the presence of 10 mol % *para*-toluene sulfonic acid (TsOH, pK_a −2.8), the substitution is sensitive to the choice of solvent, and an 83% yield of **3a** was obtained using dichloromethane (CH_2Cl_2) at 0.5 M relative to **1a** (entry 8). Selectivity improved when triflic acid (TfOH, pK_a −12) was used as the catalyst, although both TfOH and TsOH were used when evaluating substrate scope (vide infra). With both of these acids, *para*-quinone **3a** is the only observed product, whereas camphor sulfonic acid (CSA, pK_a 1.2) affords a mixture of **2a** and **3a** at incomplete conversion. A cursory screen of Lewis acidic metals (entries 15–18) returned variable results, none of which improved upon those obtained with the sulfonic acids.

Our optimized conditions for the synthesis of *ortho*- and *para*-quinones remain effective across a range of alcohols, but display different substituent constraints (Table 2). Whereas substitution under acidic conditions tolerates sterically encumbered 2° alcohols (**3g**–**3j**), decreases to both rate and efficiency are observed under basic conditions (**2g**–**2j**). For secondary alcohols, 20 mol % DBU is required, and with the exception of MeOH, complete conversion requires 12 h. Under acidic conditions, the electronic nature of the alcohol dominates reactivity, and decreases in efficiency are observed for electron deficient 1° alcohols (**3d**, **3f**). These trends are consistent with a mechanism of substitution that involves a tetrahedral intermediate adjacent to the ^{t}Bu-group of the quinone following 1,4 addition under basic conditions. Under acidic conditions, 1,2-addition to the quinone carbonyl is less sterically demanding, but is sensitive to the nucleophilicity of the alcohol (see Scheme 4 for details).

Substituted quinones lacking enolizable protons are tolerated under our standard reaction conditions (Table 3, **2k**–**m**, **3k**–**m**),